Attribution-NonCommercial 3.0 Unported (CC BY-NC 3.0)

This is a human-readable summary of the **Legal Code (the full license)**.

Disclaimer

You are free:

to Share — to copy, distribute and transmit the work

to Remix — to adapt the work

Under the following conditions:

Attribution — You must attribute the work in the manner specified by the author or licensor (but not in any way that suggests that they endorse you or your use of the work).

Noncommercial — You may not use this work for commercial purposes.

With the understanding that:

Waiver — Any of the above conditions can be **waived** if you get permission from the copyright holder.

Public Domain — Where the work or any of its elements is in the **public domain** under applicable law, that status is in no way affected by the license.

Other Rights — In no way are any of the following rights affected by the license:

- Your fair dealing or **fair use** rights, or other applicable copyright exceptions and limitations;
- The author's **moral** rights;
- Rights other persons may have either in the work itself or in how the work is used, such as **publicity** or privacy rights.

Notice — For any reuse or distribution, you must make clear to others the license terms of this work. The best way to do this is with a link to this web page.

Use this license for your own work.

This page is available in the following languages:
Castellano Castellano (España) Català Dansk Deutsch English Esperanto français hrvatski Italiano Latviski Nederlands Norsk polski Português Português (BR) Suomeksi svenska Ελληνικά Русский українська 語 (台)

Chapter 4: DRUG DEVELOPMENT

Sheila A Doggrell

School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Gardens Point, GPO Box 2434, QLD 4001, Australia

Phone +61 7 38705741 Fax +61 7 31381534 Email sheila.doggrell@qut.edu.au

Reviewer required

Key words: drug development, preclinical drug discovery, pharmacological profiling, safety and toxicity, clinical trials, ethics in clinical trials, clinical trial design, Phases in clinical trials, Therapeutics Goods Administration, Pharmaceutical Benefits Scheme

Contents

9. Drug development

From some of the sensational reporting about medicines, you might expect medicine development to be haphazard with little regard for the safety of animals or humans. This is not in fact the case. Drug development is precisely regulated and has regard for animals and humans. A general understanding of the processes of drug development should dispel many myths about drug development.

Why are drugs developed? Drugs are developed so that we can turn fatal or non-fatal diseases into a routine therapeutic exercise. For instances, before the development of anti-hypertensive drugs, hypertension was a fatal disease with people dying in a year or two of developing high blood pressure. Now, millions of people with hypertension are successfully managed long term with anti-hypertensive drugs.

Drug development is divided into **preclinical** and **clinical** drug development.

9.1 Preclinical drug discovery

Preclinical drug discovery is the process before clinical testing of drugs. The first step in preclinical drug development is the **discovery** or **synthesis** of a new drug. At least, 10,000 new molecules are discovered/synthesized for each successful new drug introduced. Extensive preclinical safety and efficacy testing of new drugs are required in animals, and this takes an average of 1.5-3 years.

There are three main ways in which new drugs are derived; chemical modification, rationale drug design, and random screening (Figure 4.1). **Serendipity** (accidental discovery of something fortunate) may also have a role in drug development.

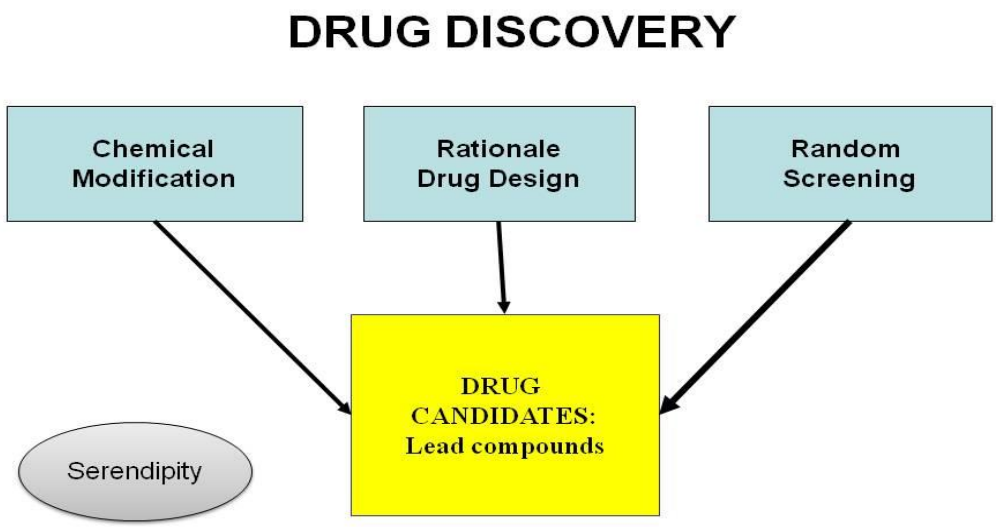

Figure 4.1 Three methods of drug discovery

An important group of drugs that were made by **chemical modification** were the diuretics. However, the initial step was serendipity; an observant physician noticed that **sulfanilamide** (antibiotic) caused a sodium bicarbonate diuresis the loss of sodium, bicarbonate and water from the kidney. Thus, it was reasoned that a sulphanilamide-like drug could be made that promoted water loss from the body. After a string of chemical modification, **chlorothiazide** was synthesised. Chlorothiazide increases sodium chloride and water excretion. Further modification of the structure of chlorothiazide led to the discovery of **frusemide**, which is a very potent diuretic. The thiazide diuretics, such as chlorothiazide, and frusemide are commonly used in the treatment of hypertension and heart failure to promote water loss.

The second method for drug discovery is **rationale drug design**, and we will consider a new example of this (zanamivir – Relenza).

Rationale drug design usually includes **computer design**, which is known as *in silico*. A computer model is made of the site that you want the drug to bind to, and then of the drug with best fit for binding. Then the chemical is synthesised, and then tested pharmacologically to determine, whether the chemicals do as predicted. A drug that was developed in this way is **zamanivir** (Relenza). Zamanivir can prevent or shorten the flu, which is a virus. Neuramidinase is an enzyme involved in viral replication, and the structure of this enzyme has been determined. The structure shows a pocket, where we may be able to get a drug in to inhibit the enzyme. Zamanivir binds in the pocket to inhibit the activity of neuramidinase, and consequently the replication of the flu virus.

A third approach to drug discovery is **random screening**. This uses high-throughput screening managed by robotics. There is random screening for biological activity. For instance, if you wanted to develop a H_2-receptor antagonist the chemicals would be screened

for activity at H_2-receptors. The screening may be of banks of previously discovered chemicals, or of natural products, or of libraries of peptides and nucleic acids.

4.2 Pharmacological profiling

Once a lead compound has been discovered (e.g. a drug with activity at a certain biding site), the compound undergoes pharmacological profiling. A large number of experiments are undertaken, mainly using animals, to determine the pharmacodynamics and pharmacokinetics of the drug. Questions asked include; Does the drug do what we expect? Does it do anything else? Is it active after oral administration? The initial profiling usually depends on the pharmacological goal e.g. anti-infectives will be tested against infectious organisms. Anti-diabetic drugs will be tested for their ability to lower blood glucose in animal models of diabetes.

4.3 Safety and toxicity

New drugs undergo extensive safety and toxicity testing in animals. This testing was increased after the **thalidomide** disaster. Thalidomide was developed as a hypnotic (calming) and anti-emetic drug in the 1950s. It was used as a hypnotic and extensively to prevent morning sickness. For severe morning sickness, it was more beneficial than any other drugs available at the time. Limited toxicity testing in rats had suggested it was safe in pregnancy. To women who took thalidomide during pregnancy, 10,000 children were born with phocomelia, which is the absence of arms or legs with hands or feet attached to body trunk. Obviously, when it was shown that thalidomide was the causative agent, it was withdrawn and litigation followed, costing the pharmaceutical company responsible to pay millions in compensation.

What was learnt from the thalidomide disaster? The animal rights movement claimed that the thalidomide disaster showed that the testing of drugs in animals was not predictive of toxicity in humans, and should be abandoned. Toxicity testing should be in humans.

There is another interpretation. Birth defects are rare in rats. Rats are more likely to reabsorb defective foeti. Closer analysis of toxicity testing of thalidomide showed lower litter numbers, which probably indicated the potential to cause birth defects in humans. More extensive toxicity in animals probably would have prevented the thalidomide tragedy. More extensive toxicity in animals is now undertaken.

This preclinical safety and toxicity testing takes two to five years, and involves the collection and analysis of lots of data. This testing is closely supervised by an independent Animal Ethics Committee that works to minimise the number of animals used, and the harm done to animals. Acute toxicity of single doses and chronic toxicity of repeated doses of drugs is often tested on mice. The effects of drugs on reproductive function and teratogenicity (ability to cause birth defects) are tested in a variety of animal species. For drugs that are going to be used long term in chronic illness, the carcinogenic potential has to be tested in animals longterm. Mutagenic potential is undertaken in bacteria.

4.4 Clinical trials – introduction

At some stage in the drug development procedure, a drug patent has to be applied for, to protect your discovery from other companies. Patents are valid for 15-17 years. During the patent, all monies made by that drug are returned to the pharmaceutical company that invested in the development. However as preclinical testing takes on average 1.5 to 5 years, and clinical trialling take 5 to 7 years on average, there may not be much time for the

developing company to recoup their investment. After a patent expires, the generic drug can be made by other companies, commonly known as generic companies. The generic companies make drugs but they do not pay towards the development of the drug. After the patent expires, the pharmaceutical company that discovered the drug, no longer receives all the money from that drug.

After successful preclinical testing, a few new drugs enter the next stage, which is clinical trialling. Clinical trials are experiments in humans to evaluate drugs, medical devices, biologics etc. Thus, clinical trials are to evaluate interventions in general. The results of clinical trials are presented to the authorities for assessment. This assessment is carried out be the Federal Drug Administration (FDA) in US, or the Therapeutic Goods Administration (TGA) in Australia. If the FDA or TGA accept that the drug does more good than harm, it is registered for clinical use. The clinical development of drugs does not stop at registration, as there is ongoing preclinical and clinical assessment. It is presently considered that it costs A$1.2 billion for a single, successful new drug.

Only about 10% of compounds that enter clinical trial are approved/registered for sale. Clinical trials are under stringent law enforced guidelines. These guidelines include ethics, which is assessed by human ethics committee, and patient consent. For patient consent, they must be fully informed in lay language of exactly what is happening in the trial. Clinical trials of drugs are often funded by pharmaceutical company with independent investigators. Without this funding, there would be little development of new drugs. There is some government funding available for clinical trials of complementary and alternative medicines in the US, which allows these medicines to be properly evaluated. Clinical trials are not quick, as they take 7-9 years.

4.5 Ethics in clinical trials

The atrocities of the Nazis on concentration camp inmates, such as cutting people and seeing how long they bled for, were investigated after World War II in Nuremberg Tribunal. The tribunal developed the Nuremberg Code, which is started the modern era of ethics. There are 4 main aspects of modern ethics. Firstly, there is **non-maleficence**, which means to do no harm. The second aspect, is the reverse of this, it is **beneficence**, which is to do good. Combining non-maleficence and beneficence means that clinical trials have to maximize benefits and minimize harm to the patient. The third aspect of ethics in clinical trials is **justice**, which means that the benefits of research should be distributed fairly, not just to the rich and powerful. The fourth aspect is **respect for person.** This has three parts, Firstly, individuals be regarded as **autonomous agents**, and their opinions and choices respected, regardless of how daft or illogical they are. The second part is **veracity**, the truth must be told to participants. Participants have to be able to understand the clinical trial, and the benefits and risks, and these are provide in a **Plain Language Statement**, prior to consent being asked for. Finally, **confidentiality**, the participants name, details etc are to be kept confidential.

Ethics are policed by IRBs, **Institutional Research Boards**, which are also known as Ethics committee. This process involves peer review of proposed research. Peer review is independent review of the proposed clinical trial to determine whether the trial is appropriate. Universities often have ethics committees both for peer reviewing animal experiments and human experiments. For instance, QUT has a **Human Research Ethics** committee, an **Animal Ethics** committee and a Biosafety committee.

4.6 Clinical trial design

There are a number of factors that make a good clinical trial design. There should be **similarity** of the control group, who do not receive the drug, with the group receiving the intervention (drug). Otherwise any difference between the control and intervention group, may be due to other differences between the groups, other than due to the drug intervention. One way of achieving similarity between groups is the r**andom assignment** of patients to control and intervention group. In initial clinical trials, the control group was untreated whereas the treated group were given the drug. This is almost guaranteed to show a beneficial effect with the drug, as people like to believe the drug is going to do them good. To avoid this, the control group are given an inert replica of the drug, which is known as the **placebo**. Placebos are very good for you! The placebo response (which means "I shall please") is 40% of relief of pain in labour, and up to 60% in relieving depression. This is the key reason for not accepting anecdotal evidence, and requiring placebo-controlled clinical trials.

Another danger in clinical trials is **observer bias**. The observer of the patients will want the patient to get better and will be looking for signs of benefit with the drug, which may or may not be present. To avoid this problem, **blinding** is used. There are two types of blinding. In **single blinded** clinical trials, only the study participants are blinded, not the investigator, and this happens when it is considered important that the investigator knows which participant has the active drug. In **double-blinded** clinical trials, neither the participants nor the investigator know who is taking the active drug. The best design for a clinical trial is the **randomized, double-blind, placebo-controlled trial**. Such a trial has the highest likelihood of revealing the truth about the effects of a drug. The randomized, double-blind, placebo controlled trial has a very simple design (Figure 4.2).

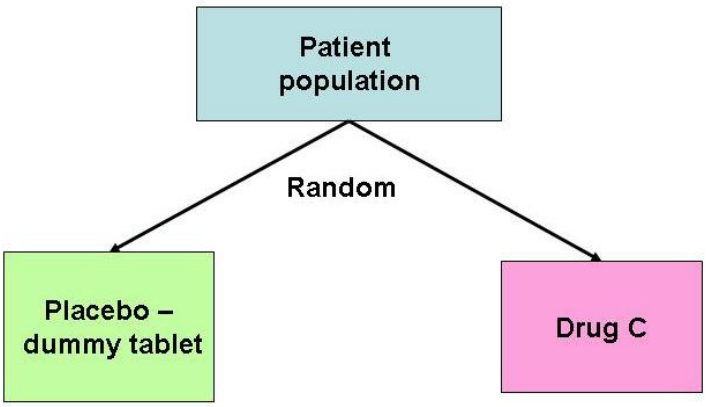

Figure 4.2 Randomized, double-blind, placebo-controlled trial (Copyright QUT, Sheila Doggrell)

In a randomized, double-blind, placebo-controlled trial, the selected patient population is randomised to either the placebo (dummy tablet) or the drug, and the health of the participants is monitored.

4.7 Phases of clinical trials

In drug development, it mandated that new drugs have to go through **4 Phases** with each phase having different requirements. Clinical trialling starts with small numbers of participants and is mainly to test safety, and only when some safety has been established, does testing in larger numbers of participants occur.

Phase I clinical trials are often performed in University Hospitals using experts in clinical pharmacology. They are open with both subject and observer knowing what is happening. Phase I clinical trials use small numbers (20-80) of healthy volunteers. The exception to this is when testing toxic drugs for cancer and HIV. As these would be toxic to healthy volunteers, the Phase I testing of cancer and HIV drugs is in patients. The dose tested in Phase I will be a small fraction of that shown to cause toxicity in animals. The main reason for the trial is to establish safety, and the trial will **measure toxicity** and, possibly, efficacy. In Phase I, provided an assay is available to measure the drug, blood samples may be taken to measure the pharmacokinetics of the drug. If a drug shows unacceptable toxicity, the clinical trialling will stop after Phase I.

Phase II clinical trials are also often performed in University Hospitals using experts. They are single-blinded i.e. they use placebo/dummy tablets to prevent the subject knowing which is active drug, but the physician does know which is the active drug. Phase II trials may have a comparison with standard treatment. If there is a standard drug available for a certain conditions, it has to be established that the new drug is better than the standard drug before it can be registered. Phase II trials are in 10-200 patients with the disease the drug is indicated for. The Phase II trial is to establish the **efficacy and toxicity** of the drugs. This information is needed for more extensive Phase III trialling. If a drug does not show efficacy in Phase II trialling, it will not go forward to Phase III.

Phase III clinical trials are usually performed in the setting the drug will eventually be used in. Thus, if a drug is to be used in hospital, it will be tested in hospital, whereas if a drug is used in general practice, it will be tested in general practice. The investigators are usually specialists in the disease being treated. Phase III trials are double-blinded; neither the observer nor the subject knows which is active drug. A third person holds the code identifying the drug, which is not broken until the trial is completed. Phase III trials enrol large numbers of patients, and are expensive. Phase III clinical trials establish **efficacy and toxicity.**

Positive results in Phase III lead to applications for registration to market the drug to the **Therapeutics Goods Administration** (TGA).

Phase IV clinical trialling is also known as **post-marketing surveillance**. Even though Phase III trials enrol large numbers of patients, this may not be large enough to detect any rare or long-term adverse effects, and this is done in Phase IV. Phase IV is under the actual conditions the drug will be used. It is monitoring safety in large numbers of patients and over longer periods of time than previous Phase. Phase IV clinical trials, especially the monitoring of adverse effects, involves, all health professionals, not just investigators.

4.8 Therapeutics Goods Administration

The Therapeutic Goods Regulations (TGA) is responsible for the quality, safety, efficacy, and timely availability of drugs and medical devices in Australia. The TGA regulates prescription, over-the-counter and complementary medicines. It usually accepts the recommendations coming from the **Australian Drug Evaluation Committee** (ADEC). ADEC is a committee of specialists that are able to evaluate pharmaceutical and chemical data, animal pharmacology and toxicology data, and clinical data. Applications are usually 100,000 pages in length, and the review by physicians/scientists takes up to 3 years. For

serious conditions, may get approval earlier in the trialling process and in a shorter time. After registration, drugs can be administered to patients outside of clinical trials at **full** cost.

4.9 Pharmaceutical Benefits Scheme

After registration, drugs are available at full cost. Only drugs that accepted into the Pharmaceutical Benefits Scheme (PBS) are subsidised as part of Medicare. Before acceptance onto the PBS, a **pharmacoeconomic** analysis is done. This analysis weighs up the benefits of the drug against the cost to the government (Medicare). Broadly speaking, they are asking "are you worth it". One of the drugs discussed extensively in the press recently is Herceptin (**trastuzumab**). Trastuzumab is very useful in certain types of breast cancer. However, the full cost is $60,000/year. Initially, women with this type of breast cancer could only have the treatment, if they paid for it. Under the PBS, trastuzumab is $33/prescription.